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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM

TXR #: 0050199
DATE: 28-MAR-2003

SUBJECT: Request for Waiver of 28-Day Inhalation Toxicity Study Requirement for **Glufosinate Ammonium**. PC Code: 128850. DP Barcode: D286444.

FROM: J. Troy Swackhammer, Chemist (ORE)
Registration Action Branch 1 (RAB1)
Health Effects Division (HED; 7509C)

THRU: G. Jeffrey Herndon, Branch Senior Scientist
RAB1/HED (7509C)

TO: Robert Forrest/Shaja Brothers; PM Team 5
Joanne Miller/Eugene Wilson; PM Team 23
Registration Division (RD; 7505C)

The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. HED completed a risk assessment dated 09-AUG-02 (D274674) for the proposed use of glufosinate ammonium on glufosinate ammonium on rice, cotton and bushberry. Prior to completion of this memo, the HED Hazard Identification Assessment Review Committee (HIARC) determined that a 3x database uncertainty factor, due to the lack of a study that measures glutamine synthetase activity in the young and adult animals, should be applied to all dietary and residential dermal, inhalation, and incidental oral exposure assessments. The HIARC also determined that for occupational and residential inhalation exposure assessments an additional 10x database uncertainty factor should be applied due to the lack of an adequate inhalation study and high concern for exposure via the inhalation route. Additionally, HED requested that a 28-day inhalation toxicity study in rats (with glutamine synthetase activity measurements in brain, kidney, liver and lung) be submitted.

Subsequent to the completion of the risk assessment, the registrant submitted a request for waiver of the 28-day inhalation study requirement to RD dated October 10, 2002. This memorandum serves to evaluate the waiver request per HED SOP 2002.01, Guidance: "Waiver Criteria for Multiple-Exposure Inhalation Toxicity Studies (August 15, 2002)."

Source of Request: "Request for Waiver of 28-Day Inhalation Toxicity Studies Data Requirement for Glufosinate-Ammonium," Aventis CropScience, October 10, 2002.

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Discussion of Four Waiver Evaluation Criteria:

- Severe Irritation and Corrosivity: Glufosinate ammonium is a crystalline powder and has an acute inhalation toxicity of III (Accession # 073916). Glufosinate ammonium is moderately irritating to the eyes, but is not a skin irritant or dermal sensitizer. A waiver is typically not granted for slight or moderately irritating active ingredients.

- Low volatility: The. HED vapor pressure threshold for waiver consideration is $<1 \times 10^{-4}$ kPa (or $<7.5 \times 10^{-4}$ mmHg) for outdoor use patterns. The vapor pressure of glufosinate ammonium is $<1 \times 10^{-6}$ kPa (MRID 44032901), so glufosinate ammonium meets this criterion.

- Large Aerosol Particle Size: The formulation containing glufosinate ammonium that was the subject of the 09-AUG-02 risk assessment is a water-soluble concentrate. Waivers will be considered for active ingredients that do not pose a significant inhalation hazard, because the particles are too large to be inhaled. To address this criterion, the registrant presented the results of two application simulations using the DropKick®model (part of AgDRIFT® model) for the fine spray droplet and fine-medium spray droplet spectrums. Details on input parameters were not provided, and the results are more general in nature, not necessarily specific to glufosinate ammonium. The information provided by the registrant is not sufficient to make an informed decision on this criterion.

- Inhalation Toxicity Category IV and an Extrapolated MOE: The acute inhalation toxicity of glufosinate ammonium is Category III (see Table 1), so the active ingredient does not meet the "Toxicity Category IV" component of this criterion. In the memorandum dated 09-AUG-02 (D274674), HED completed an occupational and an updated residential exposure and risk assessment (with extrapolated MOEs) summarized below. Toxicological endpoints used in this assessment are summarized in Table 2.

  Occupational Exposures: For this assessment, commercial pesticide handlers were expected to have short-term dermal and inhalation exposures. The target MOE for occupational inhalation exposures was 1000 per HIARC. Extrapolated MOEs for inhalation exposures ranged from 500 (mixer/loaders) to 8,900 without a dust/mist respirator and 2,500 (mixer/loaders) to 8,900 with a dust/mist respirator.

  Residential Handler Exposures: The registrant has elected to eliminate the broadcast residential use pattern in favor of spot treatment. The target MOE for residential inhalation exposures is 3000. Extrapolated MOEs for inhalation exposures by residential handlers performing spot treatments ranged from 760,000 to greater than 10^6.

  In summary, the extrapolated inhalation MOEs for occupational exposures are less than 10x the target MOE of 1000, and glufosinate ammonium is Category III for acute inhalation toxicity, therefore, this criterion is not met.

Conclusion: Based on the above evaluation against the waiver criteria, this waiver request was

presented for further review to HED's Science Advisory Committee for Exposure (ExpoSAC) on March 27, 2003. After review of the above information, ExpoSAC concluded that the 28-day inhalation study should be conducted by the registrant.

Table 1. Acute Toxicity of Glufosinate Ammonium

Study Type	Results	Toxicity Category
81-1 acute oral–rat MRID 072962	LD_{50}2000 mg/kg in males LD_{50} 1620 mg/kg in females	III
81-2 acute dermal MRID 072962	LD_{50} > 4000 mg/kg in males & females	III
81-3 acute inhalation MRID 073916	LC_{50} 1.26 mg/L in males LC_{50} 2.60 mg/L in females	III
81-4 eye irritation MRID 072962	eye irritant; corneal opacity reversible within 72 hr	II
81-5 dermal irritation MRID 072962	not a dermal irritant	IV
81-6 sensitization MRID 072962	not a dermal sensitizer	NA

Table 2. Summary of Endpoint Selection for Glufosinate Ammonium.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50)	NOAEL = **6.3** UF = **1000** **Acute RfD** = **0.0063** mg/kg/day	FQPA SF = **1X** **aPAD** = acute RfD FQPA SF = **0.0063** mg/kg/day	**[Developmental Toxicity Study in Rabbits]** LOAEL = **[20]** mg/kg/day based on **[reduced fetal body weight and increased fetal death]**.
Acute Dietary (General Population including infants and children)	Mat. NOAEL =N/A UF =**N/A** **Acute RfD** =**N/A**	FQPA SF = N/A **aPAD** = acute RfD FQPA SF = N/A	No endpoint attributable to a single exposure was identified for the general population, including infants and children.
Chronic Dietary (All populations)	NOAEL= **6.0** UF = **1000** **Chronic RfD** = **0.006** mg/kg/day	1X **cPAD** = chronic RfD FQPA SF =**0.006** mg/kg/day	**["Weight-of-evidence" approach from several studies]** NOAEL = **[6.0]** mg/kg/day based on brain glutamine synthetase inhibition and alterations in the electrocardiogram.

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term (1-30 days) **Incidental Oral**	Mat. NOAEL= **6.3** mg ai/kg/day	**Residential** MOE = **1000** **Occupational** = NA	**[Developmental Toxicity Study in Rabbits]** LOAEL = **[20]** mg/kg/day based on **[reduced food consumption, body weight and body weight gain]**.
Intermediate-Term (1 - 6 months) **Incidental Oral**	NOAEL= **6.0** mg ai/kg/day	**Residential** MOE = **1000** **Occupational** = NA	**["Weight-of-evidence" approach from several studies]** NOAEL = **[6.0]** mg/kg/day based on brain glutamine synthetase inhibition and alterations in the electrocardiogram
Short-Term (1 - 30 days) **Dermal**	Oral NOAEL= **6.3** mg ai/kg/day[a]	**Residential** MOE = **1000** **Occupational** MOE = **100**	**[Developmental Toxicity Study in Rabbits]** LOAEL = **[20]** mg/kg/day based on **[reduced fetal body weights, increased fetal mortality, reduced food consumption, and decreased body weight and body weight gain]**.
Intermediate-Term (1 - 6 months) and **Long-Term Dermal** (>6 months)	Oral NOAEL= **6.0** mg ai/kg/day[a]	**Residential** MOE = **1000** **Occupational** MOE = **100**	**["Weight-of-evidence" approach from several studies]** NOAEL = **[6.0]** mg/kg/day based on brain glutamine synthetase inhibition and alterations in the electrocardiogram
Short-Term (1 - 30 days) **Inhalation**	Oral NOAEL= **6.3** mg/kg/day[b]	**Residential** MOE = **3000** **Occupational** MOE = **1000**	**[Developmental Toxicity Study in Rabbits]** LOAEL = **[20]** mg/kg/day based on **[reduced fetal body weights, increased fetal mortality, reduced food consumption, and decreased body weight and body weight gain]**
Intermediate-Term (1 - 6 months) and **Long-Term Inhalation** (>6 months)	Oral NOAEL= 10 mg/kg/day[b]	**Residential** MOE = **3000** **Occupational** MOE = **1000**	**["Weight-of-evidence" approach from several studies]** NOAEL = **[6.0]** mg/kg/day based on brain glutamine synthetase inhibition and alterations in the electrocardiogram
Cancer	**Classification: Not likely to be carcinogen** **Q1* =** N/A		

a = Dermal absorption factor: 50%
b = Since oral values were selected 100% inhalation absorption factor (default) value should be used in route-to-route extrapolation/risk assessment.

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.